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BILATERAL OSTEOFIBROUS DYSPLASIA: A REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

Usha K. Sunkara, M.D.*
Paul D. Sponseller, M.D. #
Nancy Hadley Miller, M.D. #
Edward F. McCarthy, M.D. ^ #

Osteofibrous dysplasia is a fibro-osseous proliferation which affects the bones of children, almost always before they are ten years old. The distinctive feature of this lesion is its predilection for one site — the anterior cortex of the tibia. Almost always, the disease is unilateral. Osteofibrous dysplasia is not uncommon. Many cases have been reported in the literature. In addition to reports of one or two cases, the nine large studies of this lesion published to date document 219 cases[2,6,11,15,17,18,20,21,22]. Many cases go unrecognized because they are misdiagnosed as fibrous dysplasia or congenital tibial bowing. Furthermore, because some lesions are asymptomatic, they are not diagnosed at all.

Bilateral osteofibrous dysplasia, by contrast, is extremely rare. We are aware of only five cases that have been documented in the literature. We wish to report our experience with two additional cases and explore the significance of bilaterality to the pathogenesis of this disorder.

Case 1

A four week old female infant, the product of a forty week gestation, was noted to have non-tender bowing of her left tibia at the time of birth. Radiographs of her lower extremities showed metaphyseal-diaphyseal lucent defects in both proximal tibias with anterior bowing and periosteal reaction of the left tibia. The radiographic diagnosis was bilateral osteofibrous dysplasia. On follow-up examination, the patient developed shortening of the right tibia and progressive bowing of the left tibia. At eight months of age, the lucencies in the right tibia had grown (Figure 1) and there was a pathologic fracture through the lesion on the left (Figure 2). A resection of the left tibial lesion with allograft replacement was performed. Tissue removed from the lesion was consistent with osteofibrous dysplasia, although cytokeratin stains were negative. The allograft has failed to heal in the two years following surgery. In fact, lytic lesions have appeared extensively throughout the graft. Further surgery is planned. The right lesion continues to grow slowly, although this tibia has remained structurally intact.

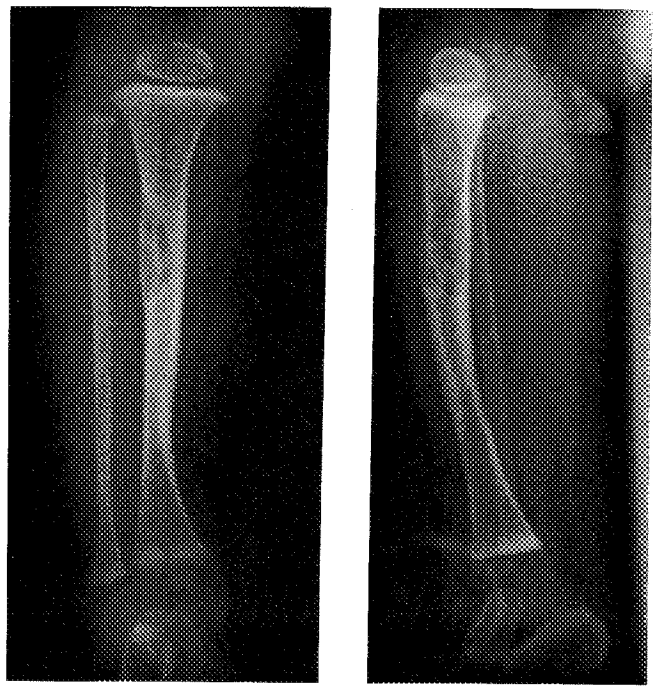

Figure 1. Right tibia of patient 1 at age eight months.

Case 2

A three year old boy was first observed to have right anterior tibial swelling at age two. Radiographs of his long bones showed cortex-based lucencies in both the left (Figure 3) and the right (Figure 4) tibias. The radiographic diagnosis was bilateral osteofibrous dysplasia. Family history was remarkable for a mother with spherocytosis and a father with β-thalassemia minor. Hematologic work-up revealed microcytosis without ane-

* Department of Medicine, Sinai Hospital of Baltimore, Baltimore, MD
# Department of Orthopaedic Surgery, Johns Hopkins Hospital, Baltimore, MD
^ Department of Pathology, Johns Hopkins Hospital, Baltimore, MD

Corresponding Author:
Edward F. McCarthy, M.D.
Department of Pathology # 306
600 North Wolfe Street Baltimore, MD 21287
Phone: (410) 614-3653

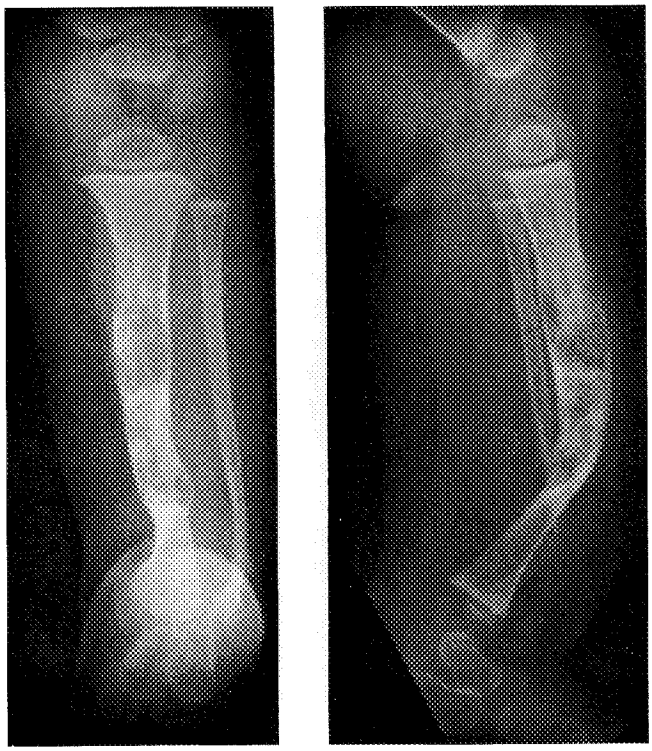

Figure 2. Left tibia of patient 1 at age eight months. A pseudarthrosis is present.

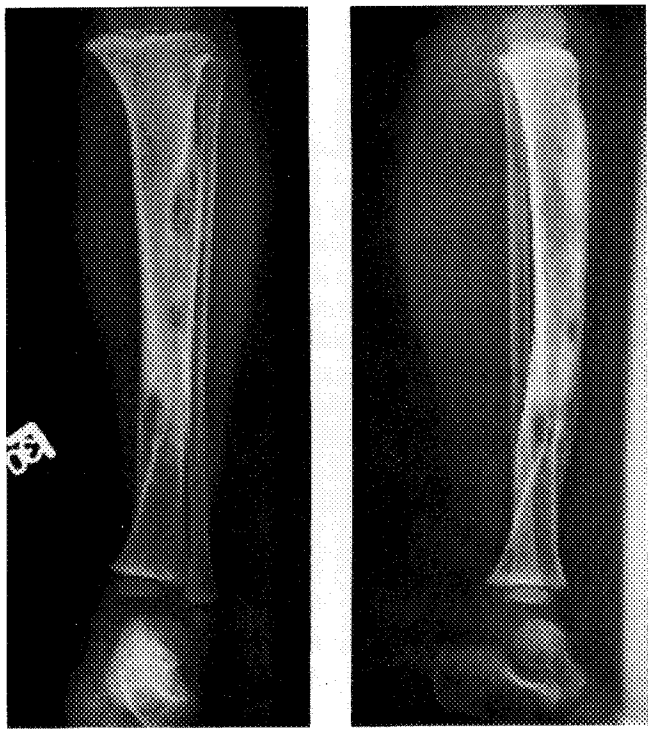

Figure 3. Left tibia of patient 2 at age three years.

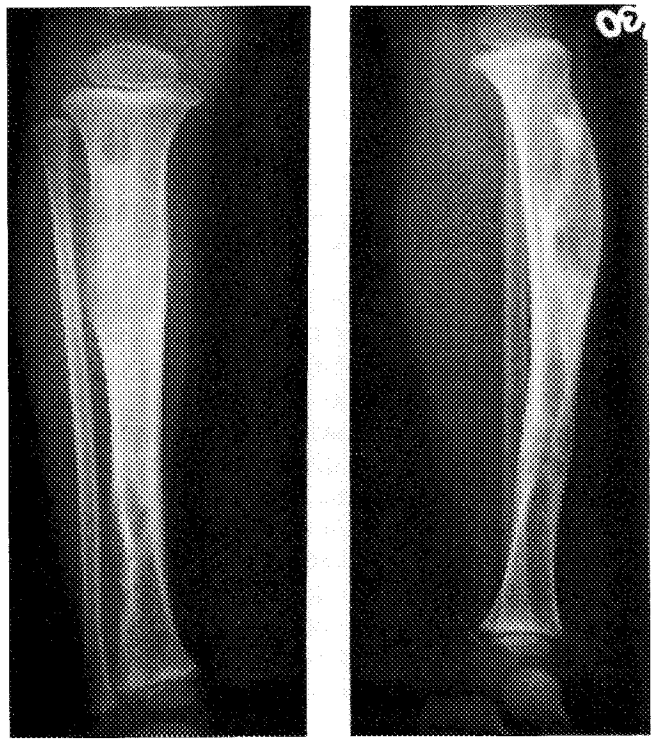

Figure 4. Right tibia of patient 2 at age three years.

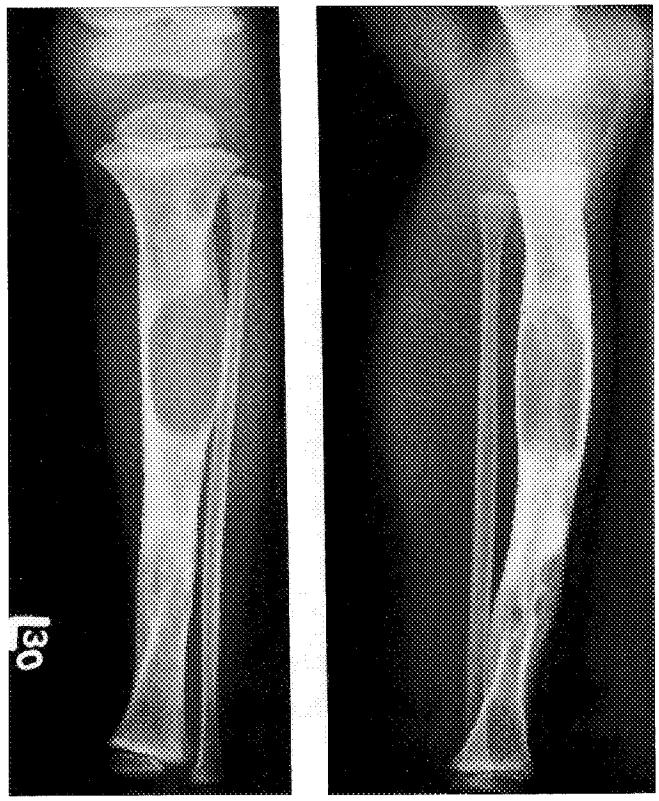

Figure 5. Left tibia of patient 2 at age four years. There is a large lytic component.

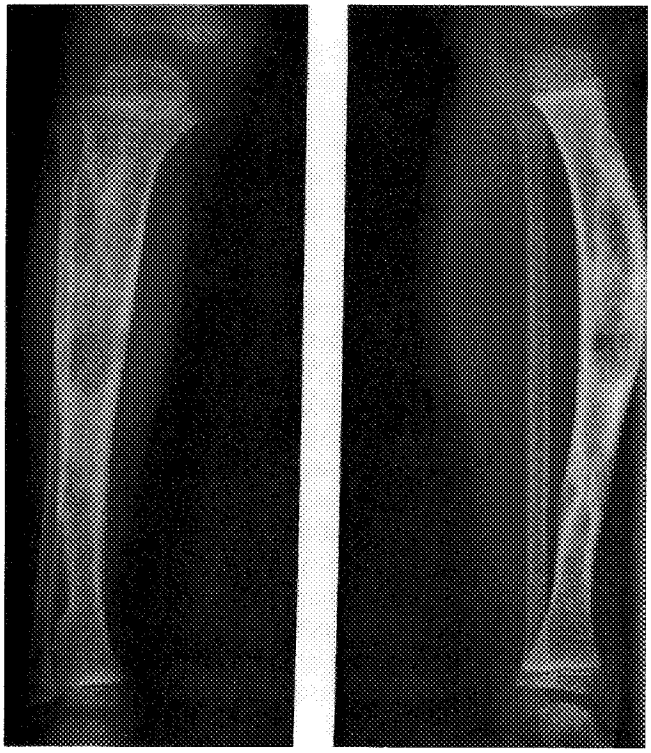

Figure 6. Right tibia of patient 2 at age four years.

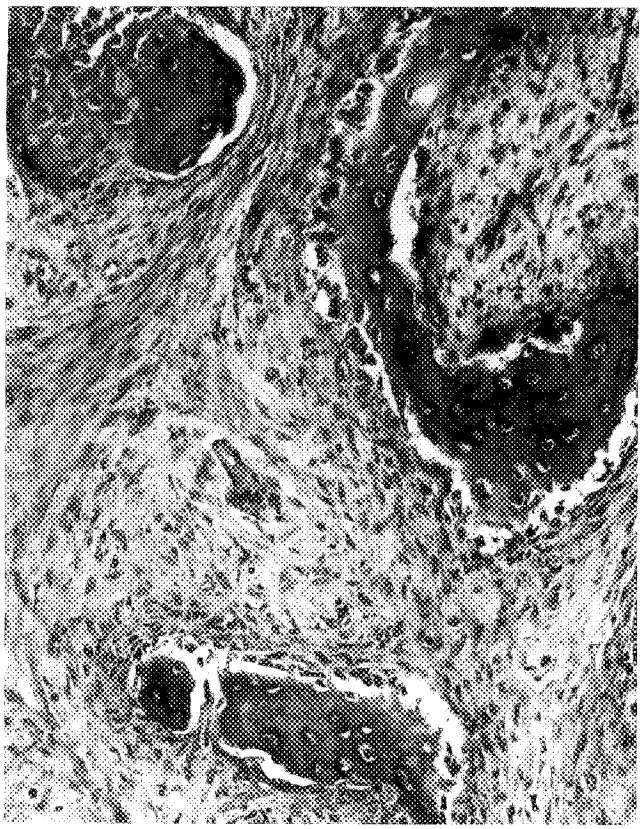

Figure 7. Photomicrograph of tibial biopsy of patient 2. A fibro-osseous lesion with woven bone lined by osteoblasts. (H & E, x320)

mia consistent with thalassemia trait. By age four, lesions in both tibias had grown, the left (Figure 5) greater than the right (Figure 6). An expansile lytic component of the left lesion prompted a biopsy. The pathologic diagnosis was osteofibrous dysplasia (Figure 7). Keratin stains were positive. The patient subsequently developed a fracture through the left lesion which is slowly healing with an external brace.

Discussion

Osteofibrous dysplasia was first described by Frangenhein in 1921 as *congenital osteitis fibrosa*[12]. In 1936, Compere noted a relationship between this lesion, which he called *localized osteitis fibrosa*, and congenital pseudarthrosis[10]. This relationship was further explored by Aegerter in 1950, who believed that this tibial lesion was a form of fibrous dysplasia[1]. He postulated that the tibial process was a manifestation of neurofibromatosis, a genetic disease sometimes complicated by congenital pseudarthrosis. In 1966, Kempson's accurate histologic and electron microscopic study distinguished this process from fibrous dysplasia[16]. He called this lesion *ossifying fibroma of long bones* because of the histologic similarity to ossifying fibroma of the facial bones. However, it was not until Campanacci's description of thirty-five cases in 1976[5] that the clinical, radiographic, and histologic spectrum of this disorder was recognized. Campanacci called this lesion osteofibrous dysplasia to emphasize its non-neoplastic nature.

Osteofibrous dysplasia has a distinct clinical presentation. This disorder is almost exclusively limited to the tibia. Most patients present between five and ten years of age. In rare cases, a lesion may not be recognized until the patient is about age thirty. Also, lesions are sometimes diagnosed in the neonatal period. Patients typically present with painless swelling over the mid-tibia, and anterior bowing is often present.

The distinctive radiographic feature of osteofibrous dysplasia is multiloculated, intracortical lucencies which are almost always centered on the anterior diaphyseal cortex. Varying amounts of sclerotic bone are usually present. Radiographs reveal a spectrum of severity. In some cases, lesions are small (one to two cm) and remain stationary. Other lesions involve most of the tibial shaft. Often, in these severe cases, the lesions expand and coalesce until skeletal growth is complete. In addition, the ipsilateral fibula may be focally involved in as many as 17 percent of cases[22]. Twelve to 33 percent of patients develop a pseudarthrosis[6,20].

Histologically, osteofibrous dysplasia is characterized by irregular new bone trabeculae amidst cellular fibrous tissue, a pattern reminiscent of fibrous dysplasia. How-

ever, unlike the trabeculae of fibrous dysplasia which seem to appear de novo in the fibrous stroma, the trabeculae of osteofibrous dysplasia are lined by plump osteoblasts. The trabeculae of osteofibrous dysplasia are arranged in a zonal pattern; the center of the lesion is predominantly fibrous while the periphery contains more new bone. This zonal pattern is not a feature of fibrous dysplasia. The most distinctive histologic feature of osteofibrous dysplasia is keratin positive cells. Ninety-three percent of lesions contain scattered spindle cells which stain immunocytochemically for cytokeratin[22]. Having no other epithelial features, these cells are not apparent with a routine hematoxylin and eosin (H & E) stain.

The predilection of osteofibrous dysplasia for the tibia and the presence of keratin positive cells has led to considerable speculation about its relationship to adamantinoma[11,21]. Adamantinomas also occur almost exclusively in the tibia and contain keratin positive cells, although to a much greater degree. Moreover, adamantinomas often contain fibro-osseous tissue identical to the characteristic tissue of osteofibrous dysplasia. The exact nature of this relationship is uncertain. However, despite many similarities, the behavior of these two lesions is quite different. Adamantinomas are malignant neoplasms which occur in patients who are almost always older than age twenty[11]. Although, they have some radiographic similarities to osteofibrous dysplasia, areas of cortical destruction and medullary canal involvement are common. In addition, soft tissue masses are often present, and metastases occur in about 30 percent of cases[14].

Osteofibrous dysplasia, by contrast, is a non-neoplastic, self-limited process. There has been no reported case of transformation of this disease into an adamantinoma. Lesions grow slowly until skeletal maturity; thereafter, they stabilize. Small lesions sometimes disappear spontaneously. Large lesions, even those which have resulted in architectural deformity, stop growing. Therefore, if at all possible, surgical removal of these lesions should be avoided[6]. Curettage during the proliferative phase is almost always followed by recurrence[18]. Surgery should be reserved for those lesions with severe deformity or pseudarthrosis.

Recently, a new point on the osteofibrous dysplasia —adamantinoma spectrum has been identified. Some lesions, clinical and radiographically identical to severe osteofibrous dysplasia, contain discrete nests of epithelial cells, although they are not as prominent as in adamantinomas. These lesions, called differentiated adamantinomas, may represent burned out cases of severe osteofibrous dysplasia[11,15]. Alternatively, they may represent an intermediate stage between osteofibrous dysplasia and classic adamantinoma.

In nearly all cases, osteofibrous dysplasia involves only one tibia. The involvement of both tibias has been

TABLE 1
Bilateral Osteofibrous Dysplasia
Summary of Cases

	Sex	Age	Treatment	Follow-up	Status
1 Case 1	F	4 weeks	(L) resection with allograft (R) no treatment	2 years	failed allograft active lesion
2 Case 2	M	3 years	(L) Bracing (R) no treatment	2 years	active lesion active lesion
3 Companacci and Laus (6)			No clinical information		
4 Companacci and Laus (6)			No clinical information		
5 Nakashima et al. (18)	M	2 years 3 years	(L) currettage & bone graft (R) currettage	10 years	healed healed
6 Castellote et al. (9)	F	6 years	(L) Excision (R) No treatment	6 years	healed stable
7 Ozaki et al. (19)	F	18 months	(R) currettage & bone graft (L) no treatment	5 years	healed resolved spontaneously

reported only five times (Table 1). Two of Companacci and Laus' thirty-five patients had bilateral involvement[6]. In one of these patients, both fibulas were also involved. No clinical details were provided. Nakashima et al. reported twelve cases of osteofibrous dysplasia, one of which had bilateral disease[18]. The lesion in one tibia was recognized at age two and the other at age three. Both lesions healed after curettage (one with bone grafting). In a report by Castellote et al. of two patients with osteofibrous dysplasia, one had bilateral disease[9]. The patient was a six year old girl with small lesions. One lesion was excised and the other was followed. By age fourteen, both tibias showed only mild anterior bowing with foci of sclerosis; a few minute lytic areas were present on one side. The final report of bilateral osteofibrous dysplasia was by Ozaki et al.[19]. These authors described an eighteen month old girl with bilateral tibial lesions as well as lesions in both ulnas and one fibula. Curettage of one tibial lesion resulted in healing. All other lesions disappeared spontaneously.

The two patients we are reporting have severe disease in one tibia and moderate disease in the other. The severely involved tibia in both patients fractured. Patient 1 required an allograft which has not healed. Patient 2 fractured through a lytic focus that was biopsied. This fracture is healing, but the patient requires external bracing. Because our patients are now only age three and five and one-half, we expect continued growth of these lesions. From these two patients and the five previously reported, it appears that lesions in bilateral osteofibrous dysplasia show a spectrum of severity similar to mono-stotic disease.

Bilaterality in osteofibrous dysplasia is further evidence of a close relationship to fibrous dysplasia, a relationship that suggests a similar pathogenesis. Histologic similarities have long been recognized. Both lesions consist of woven bone in a cellular fibrous background. In fact, a few lesions of osteofibrous dysplasia evolve into a radiographic pattern more characteristic of fibrous dysplasia[20]. Furthermore, similar cytogenetic abnormalities have been demonstrated in lesions of both osteofibrous dysplasia and fibrous dysplasia[3,4]. These observations, coupled with histologic similarities, have led to the hypothesis that osteofibrous dysplasia is a variant of fibrous dysplasia[7,20]. Bilaterality in osteofibrous dysplasia, as demonstrated by these seven cases, possibly correlates with the polyostotic variant of fibrous dysplasia. Twenty percent of patients with fibrous dysplasia have involvement of more than one bone. Some of these patients also have endocrine abnormalities and cafe-au-lait spots, a disorder known as the McCune-Albright syndrome. Polyostotic fibrous dysplasia is now known to be a genetic disorder caused by a mosaic state of an activating mutation in the GNAS 1 gene. This gene codes for an adenosinetriphosphate (ADT)-dependent G protein[23]. In addition, over expression of the C-fos proto-oncogene has been noted in the bone of eight patients with fibrous dysplasia[8]. The many similarities of osteofibrous dysplasia and fibrous dysplasia suggests that osteofibrous dysplasia may also have a genetic cause.

Another association which further suggests a genetic origin of osteofibrous dysplasia is an overlapping feature with neurofibromatosis 1—the development of pseudarthrosis. Neurofibromatosis 1, the most common single gene disorder in humans, is due to a mutation in the NF-1 tumor suppressor gene located on chromosome seventeen[13]. At least 50 percent of cases of congenital pseudarthrosis are associated with this genetic disorder. Pseudarthrosis also occurs in as many as one-third of the patients with osteofibrous dysplasia. Furthermore, the spectrum of severity of pseudarthrosis associated with neurofibromatosis parallels, in many ways, the spectrum of bone changes in osteofibrous dysplasia. Some lesions are very mild and present only with anterior tibial bowing. Other lesions are more severe and are fractured at birth. Often, these severe lesions do not heal despite a wide variety of surgical interventions. It is highly probable that many lesions classified as congenital pseudarthrosis, especially those with cystic change, are actually examples of osteofibrous dysplasia.

In summary, we have described two cases of bilateral osteofibrous dysplasia, a presentation that has been noted only five other times. The occurrence of bilaterality suggests a kinship with polyostotic fibrous dysplasia, a known genetic disorder. This kinship, as well as similarities to congenital pseudarthrosis seen in neurofibromatosis 1, suggests a possible genetic origin of osteofibrous dysplasia.

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